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Effect of Dobutamine Stress Echocardiography on Mitral Regurgitation

SHEILA K. HEINLE, MD, FACC, FRANK D. TICE, MD, JOSEPH KISSLO, MD, FACC
Durham, North Carolina

Objectives. **This study was performed to examine the effect of dobutamine stress echocardiography on mitral regurgitation and to test the hypothesis that mitral regurgitation will increase in patients with an ischemic response.**

Background. **New or worsening mitral regurgitation during stress testing has been proposed as a marker of ischemia. However, it is unclear whether ischemia induced by dobutamine is associated with mitral regurgitation because the hemodynamic effects of dobutamine may vary with regard to mitral regurgitation, depending on left ventricular function and maximal dose attained.**

Methods. **Dobutamine stress echocardiography was performed in 102 consecutive patients with suspected or known coronary artery disease. Color flow Doppler was used to determine the presence and change in mitral regurgitation at baseline and peak dobutamine infusion (up to 40 μg/kg body weight per min). The mitral regurgitation color flow Doppler area was semiquantitatively graded as mild (<4 cm^2), moderate (4 to 8 cm^2) or severe (>8 cm^2). Patients were assigned to ischemic and nonischemic groups according to the dobutamine stress echocardiographic results.**

Results. **The two groups achieved the same maximal dose and demonstrated similar blood pressure and heart rate responses to dobutamine infusion. Only two patients developed new mitral regurgitation during dobutamine infusion, and both had a normal dobutamine echocardiographic result. More patients without ischemia had no mitral regurgitation compared with patients with ischemia. There was an insufficient number of patients with coronary angiographic data to determine the effects of mitral regurgitation on the sensitivity and specificity of dobutamine stress echocardiography. Of 23 patients with a rest ejection fraction <50%, 61% had an improvement in mitral regurgitation grade compared with 25% of patients with a rest ejection fraction ≥50% ($p < 0.02$).**

Conclusions. **These data indicate that although dobutamine infusion often improves mitral regurgitation in patients with left ventricular dysfunction during stress echocardiography, it does not induce or worsen mitral regurgitation in those who demonstrate an ischemic response. Future studies are necessary, with larger numbers of patients, to determine the effects of mitral regurgitation on the sensitivity and specificity of dobutamine stress echocardiography.**

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Dobutamine stress echocardiography has emerged as an important alternative method for evaluating patients with coronary artery disease (1–4). A potential advantage of this technique over nuclear imaging methods is the ability to simultaneously assess mitral regurgitation by color flow Doppler. It has been suggested that the development of new mitral regurgitation improves the sensitivity of dobutamine stress echocardiography for detecting coronary artery disease (3). Dobutamine has beneficial hemodynamic effects, particularly in the failing heart (5–7) and in patients with chronic mitral regurgitation (8,9). However, the effect of stress doses of dobutamine on mitral regurgitation is unclear. It is also not currently known how the beneficial hemodynamic effects interact with dobutamine-induced ischemia to affect mitral regurgitation.

This study was performed to examine the effect of dobutamine stress echocardiography on mitral regurgitation and to test the hypothesis that mitral regurgitation will increase in patients with an ischemic response during dobutamine stress echocardiography.

Methods

Patients. The study included 102 consecutive patients (44 men, 58 women; mean [±SD] age 62 ± 14 years, range 29 to 94) who were referred for dobutamine stress echocardiography to evaluate known or suspected coronary artery disease. Patients with unstable angina, advanced symptoms of congestive heart failure, uncontrolled hypertension, hypertrophic cardiomyopathy, critical aortic stenosis or a history of sustained ventricular arrhythmia were excluded. The indications for dobutamine stress echocardiography included chest pain in 61%, preoperative risk assessment in 13%, functional significance of known coronary lesions in 9%, myocardial infarction

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Address for correspondence: Dr. Sheila K. Heinle, Assistant Professor of Medicine, Division of Cardiology, Box 31152, Duke University Medical Center, Durham, North Carolina 27710.

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in 4%, revascularization in 2% and other miscellaneous reasons in 11%. No cardiac medications were withheld before the study. Beta-adrenergic blocking agents were taken by 31% of patients, calcium channel blocking agents by 39% and nitrates by 55%.

Dobutamine stress echocardiography. Baseline hemodynamic, electrocardiographic (ECG) and echocardiographic data were recorded. Dobutamine was then infused intravenously in an incremental regimen of 5, 10, 20, 30 and 40 μg/kg body weight per min for 3 min at each dose. End points of the infusion included achievement of 85% of age-predicted maximal heart rate, diagnostic ST segment depression, new wall motion abnormality, significant symptoms or arrhythmia, severe hypertension (systolic blood pressure >200 mm Hg or diastolic blood pressure >110 mm Hg), severe hypotensive response (decrease in blood pressure from baseline >20 mm Hg) or completion of the protocol. If the target heart rate was not achieved, atropine was administered intravenously in incremental doses to a maximal total dose of 2 mg. Intravenous lopressor and esmolol were available to treat persistent adverse effects. A 12-lead ECG was obtained at every 3-min stage. Heart rate and blood pressure were recorded every 1 to 2 min by automated cuff monitor.

Two dimensional echocardiography (Hewlett-Packard 77020, Interspec Apogee CX 200) was performed in the parasternal long-axis, short-axis and apical four- and two-chamber views at baseline, 2 min into low dose (10 μg/kg) and peak dose and at least 5 min after the dobutamine infusion was terminated. Mitral regurgitation was evaluated by color flow Doppler imaging (2.5-MHz transducer) in the parasternal long-axis and apical views at baseline and at peak dose. The gain settings were standardized initially by increasing the setting until color signals were seen outside the flow area and then reduced until these extraneous signals disappeared. The optimized gain settings and depth were maintained for each patient throughout the study. The color map was set to optimize the color variance signal. Semiquantitative analysis of mitral regurgitation was performed by two independent observers and was based on the total regurgitant jet area and graded as mild (<4 cm^2), moderate (4 to 8 cm^2) and severe (>8 cm^2), as previously described (10). A significant change in mitral regurgitation was defined as a change of at least one grade compared with baseline.

Stress echocardiographic analysis was performed from a digital quad screen display (Nova Microsonics Image Vue) by two independent experienced observers who had no knowledge of the clinical and angiographic data. The left ventricle was divided into 16 segments according to American Society of Echocardiography criteria (11). Results of the dobutamine stress echocardiogram were considered normal if all segments that were normal at baseline showed a hyperdynamic response with increased systolic wall thickening. The development of new or worsening regional asynergy, defined as hypokinesia, akinesia or dyskinesia during dobutamine stress, was considered consistent with ischemia. The persistence of baseline asynergy, without worsening, was considered to be consistent with infarction without inducible ischemia.

Table 1. Hemodynamic Response During Dobutamine Stress Echocardiography

	Baseline (mean ± SD)	Peak Dose (mean ± SD)	p Value
Heart rate (beats/min)	76 ± 15	124 ± 19	< 0.0001
Systolic BP (mm Hg)	140 ± 26	153 ± 33	0.0001
Diastolic BP (mm Hg)	75 ± 14	69 ± 17	0.003
Rate-pressure product (beats/min × mm Hg × 10^3)	10.7 ± 3	19.9 ± 5	< 0.0001
Ejection fraction (%)	53.5 ± 16	63.9 ± 13	< 0.0001

There was a statistically significant increase in heart rate, systolic blood pressure (BP), rate-pressure product and ejection fraction and a decrease in diastolic blood pressure during dobutamine stress echocardiography.

Left ventricular function was quantitated at baseline by echocardiographic analysis in the apical views according to the modified Simpson's rule.

Coronary angiography. Coronary angiography was performed by the Judkins technique within 2 weeks of the dobutamine stress echocardiogram in 25 patients. Multiple angulated views of all coronary segments were obtained at 30 frames/s with use of a Philips S-ray system. Visual estimates of coronary artery stenosis severity were determined by consensus agreement of at least two experienced angiographers who had no knowledge of the dobutamine echocardiographic results. Significant coronary artery disease was defined as a lumen narrowing of ≥75%.

Statistical analysis. Dichotomous variables were analyzed by the Fisher exact test. Continuous variables were examined using paired and unpaired Student *t* tests. A p value of 0.05 defined statistical significance.

Results

Dobutamine stress echocardiography. Patients were assigned to two groups according to dobutamine stress echocardiographic results. Group I included patients with no ischemia (normal or infarcted myocardium, n = 69); group II included patients with an ischemic result (ischemia or mixed ischemia and infarct, n = 33). The maximal dose achieved was not significantly different between the two groups of patients. Atropine was administered in 22 patients (22%). Persistent adverse effects of chest pain and arrhythmia necessitated treatment with intravenous beta-blockers in two patients.

Hemodynamic response to dobutamine infusion. Mean heart rate, rate-pressure product and ejection fraction increased significantly from baseline to peak dose in response to dobutamine infusion (Table 1). When the hemodynamic response to dobutamine was analyzed according to the dobutamine stress echocardiographic results, there was no significant difference between patients who did or did not develop ischemia (Table 2). A slight difference in these hemodynamic variables could not be excluded without studying many more patients.

Mitral regurgitation. By color flow Doppler, no mitral regurgitation was present in 50 patients at baseline or at peak

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Table 2. Hemodynamic Response by Dobutamine Stress Echocardiographic Result

	No Ischemia (mean ± SD)	Ischemia (mean ± SD)	p Value
Change in heart rate (beats/min)	47 ± 20	49 ± 21	0.7
Change in SBP (mm Hg)	14 ± 34	9 ± 28	0.5
Change in DBP (mm Hg)	−4 ± 19	−6 ± 16	0.8
Change in EF (%)	11 ± 17	10 ± 25	0.9

Change in heart rate, systolic (SBP) and diastolic (DBP) blood pressure and ejection fraction (EF) from baseline to peak dobutamine infusion.

Table 3. Effect on Mitral Regurgitation by Dobutamine Stress Echocardiographic Result

	Ischemia	No Ischemia	p Value
No MR (n = 50)	37	13	0.01*
No change in MR (n = 28)	15	13	0.84
Decrease in MR (n = 22)	15	7	0.11
Increase in MR (n = 2)	2	0	†

*Statistically significant. †A p value calculation with n = 2 would be misleading. Data presented are numbers of patients in group. MR = mitral regurgitation.

dobutamine infusion (Table 3). Of the 50 patients with baseline mitral regurgitation, the grade was unchanged in 28 patients at peak dose (Fig. 1), whereas there was a decrease in mitral regurgitation in 22 patients (Fig. 2). New mild mitral regurgitation developed in two patients only, both of whom had a normal dobutamine echocardiographic findings (Table 3). Posterior or lateral ischemia developed in three patients with documented coronary artery disease, none of whom had worsening mitral regurgitation. Interobserver and intraobserver variability for assigning mitral regurgitation grade semiquantitatively, by color flow Doppler, were 10% and 5%, respectively. Eccentric mitral regurgitation jets were seen in 5 patients (5%).

Mitral regurgitation and left ventricular function. Ejection fraction at rest was quantitated in all but two of the patients with baseline or new mitral regurgitation during dobutamine stress echocardiography. Patients were assigned to two groups on the basis of rest left ventricular ejection fraction (ejection fraction <50% [mean 35 ± 11%] and ≥50% [mean 63 ± 9%]]). Blood pressure and heart rate responses to dobutamine infusion were not significantly different in patients with a low rest ejection fraction compared with those with a normal ejection fraction (Fig. 3). However, during dobutamine infusion, there was a significantly greater increase in ejection fraction (mean 22 ± 17%) in the group with a low rest ejection fraction than in the group with a high rest ejection fraction (mean 2 ± 16%) ($p < 0.0001$). The maximal dobutamine dose was not significantly different between these two groups. Although none of the patients with a rest ejection fraction <50% had worsening of mitral regurgitation, in two patients (7%) with a rest ejection fraction ≥50%, mitral regurgitation worsened during dobutamine stress echocardiography (Fig. 4) ($p = 0.49$). Twenty-three patients had an ejection fraction <50%, of whom 61% had improvement in mitral regurgitation (Fig. 4) with dobutamine infusion compared with 25% of 27 patients with a rest ejection fraction ≥50% (Fig. 4) ($p = 0.02$).

Coronary angiography. Of 25 patients who underwent coronary angiography, 18 were found to have significant coronary artery disease. Of these 18 patients, 17 (94%) had ischemia, infarction or ischemia and infarction during dobutamine stress echocardiography. There were significant coronary lesions in 11 left anterior descending, 12 left circumflex and 9 right coronary artery territories. A decrease in ejection fraction was observed during dobutamine infusion in 7 of the 18 patients with significant coronary artery disease. Only 7 (15%) of 47 patients with normal dobutamine stress echocardiographic findings underwent coronary angiography, thus limiting assessment of the specificity of dobutamine stress echocardiography.

Dobutamine stress electrocardiography. The ECG revealed significant ST segment depression during dobutamine infusion in 6% of patients with normal dobutamine echocardiographic results compared with 21% of patients with ischemic results. Twenty-seven percent of patients with echocardiographic infarction also had positive ECG findings.

Discussion

A previous study by Mazeika et al. (3) suggested that the development of new mitral regurgitation during dobutamine stress echocardiography improves the sensitivity of this test for detecting coronary artery disease from 78% to 81% without a decrease in specificity (3). However, studies to date have an insufficient number of patients with coronary angiographic data to make definitive conclusions about the effect of new mitral regurgitation on the sensitivity and specificity of dobutamine stress echocardiography. Therefore, it was not the purpose of this study to answer this question; rather, we wished to examine the effect of dobutamine stress echocardiography on mitral regurgitation. The major finding in the current study was that dobutamine stress echocardiography induces new or worsening mitral regurgitation in very few patients. Furthermore, no patient who developed wall motion abnormalities consistent with ischemia exhibited new or worsening mitral regurgitation.

Mechanisms of mitral regurgitation. This study confirms the beneficial effect of dobutamine on mitral regurgitation in patients with left ventricular dysfunction. The mechanism of this beneficial effect remains unclear, although it may be related to a decrease in afterload or mitral orifice size that results from the vasodilatory and inotropic effects of dobutamine (8). Kaul et al. (12) reported that incomplete mitral leaflet closure led to ischemic mitral regurgitation even without regional dyskinesia but with global left ventricular dysfunction. The latter mechanism may explain the benefit of the inotropic effect of dobutamine on mitral regurgitation in

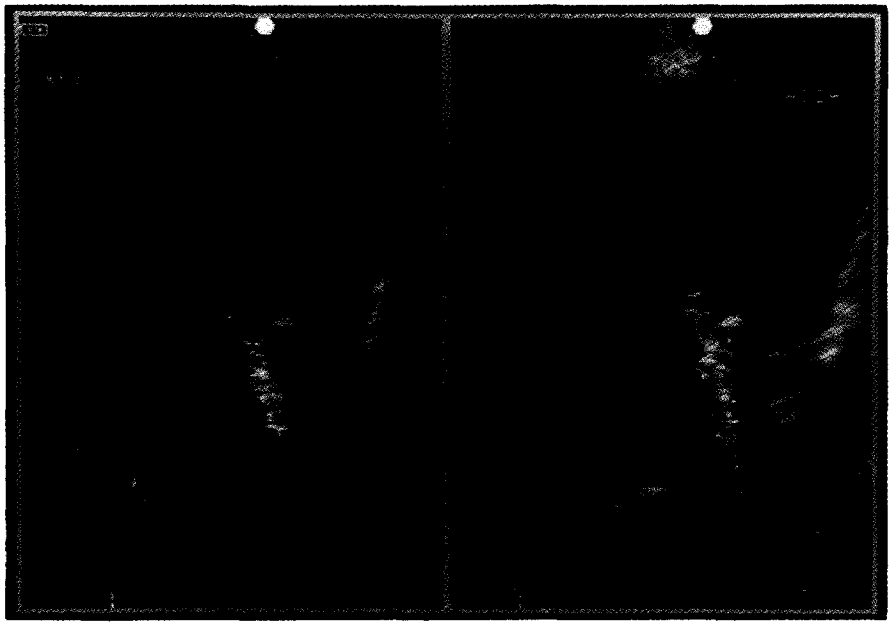


Figure 1. No change in mitral regurgitation grade from baseline to peak stress was observed despite development of anterior and anteroseptal ischemia during dobutamine stress echocardiography.

patients with left ventricular dysfunction with or without ischemia.

Study limitations. Most of the patients in this study did not undergo coronary angiography. Therefore no reference standard was available to assess coronary artery disease status. However, the high sensitivity and specificity of dobutamine stress echocardiography for detecting coronary artery disease has been well documented (1–4). Previous studies (10,13,14) have shown good correlation between mitral regurgitation color jet area and the angiographic grade of mitral regurgitation. However, the color flow jet area does not correlate well with angiographic estimates of regurgitant fraction or volume (10,13), which is not surprising because color flow Doppler areas do not take spatial or temporal variability into account. Furthermore, it is generally assumed that the larger the jet area, the greater the severity of mitral regurgitation. However, technical and anatomic factors may influence the color jet area. It has been demonstrated that gain settings, pulse repetition frequency, transducer frequency, scanning depth, and filter settings can all influence the color Doppler jet area (15–18). We attempted to minimize this potential source of variability by optimizing these technical factors during the baseline examination and maintaining these settings on the same ultrasound machine for the peak dobutamine dose image. In this study, interobserver variability in assessing the grade of mitral regurgitation by color flow Doppler areas was well within

Figure 2. Mitral regurgitation grade improved from moderate to mild in this patient with a rest left ventricular ejection fraction <50%.

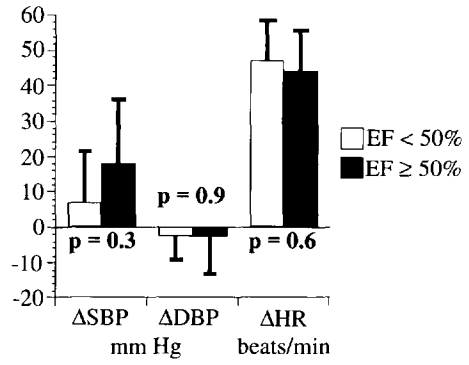
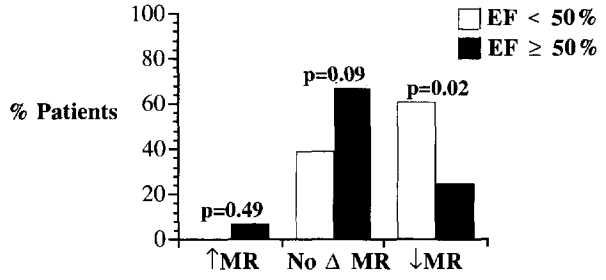


Figure 3. Hemodynamic effects of dobutamine on left ventricular function. No significant difference (Δ) was observed in heart rate (HR) or systolic (SBP) or diastolic (DBP) blood pressure response to dobutamine infusion in patients with an ejection fraction (EF) < 50% versus those with an ejection fraction ≥50%.

previously reported ranges (19,20). The color Doppler jet area of eccentric mitral regurgitation may underestimate the regurgitant volume because the impingement of the jet on the atrial wall results in decreased momentum (21,22). In this study only five patients had eccentric mitral regurgitation jets. As with other studies of color flow Doppler estimates of mitral regurgitation, the present study also lacks a reliable reference standard method for comparison. Contrast ventriculography also has technical limitations with regard to evaluating mitral regurgitation (23,24). The present study is a preliminary analysis of the effect of dobutamine stress echocardiography on mitral regurgitation. Future studies on this topic should be performed with quantitative Doppler methods and include larger numbers of patients with coronary angiographic data.

Conclusions. It has been previously suggested (25) that detection of ischemic mitral regurgitation has important prognostic implications that affect management decisions. However, on the basis of the results of this study, dobutamine stress echocardiography does not identify patients with ischemic mitral regurgitation. In fact, very few patients develop new or worsening mitral regurgitation during dobutamine infusion even with development of new or worsening wall motion abnormalities that are consistent with an ischemic response. To the contrary, this study demonstrated that many patients have an improvement in mitral regurgitation during dobutamine stress echocardiography, particularly those with preexisting left ventricular dysfunction. Future studies with larger numbers of patients would be necessary to assess the effect of mitral regurgitation on the sensitivity and specificity of dobutamine echocardiography.

Figure 4. Effects of dobutamine on mitral regurgitation (MR) and left ventricular function. Mitral regurgitation grade did not change (No Δ) or worsen (**upward arrow**) significantly in patients with a rest left ventricular ejection fraction <50% or ≥50%. However, significantly more patients with an ejection fraction <50% had improvement (**downward arrow**) in mitral regurgitation than those with a normal ejection fraction.



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